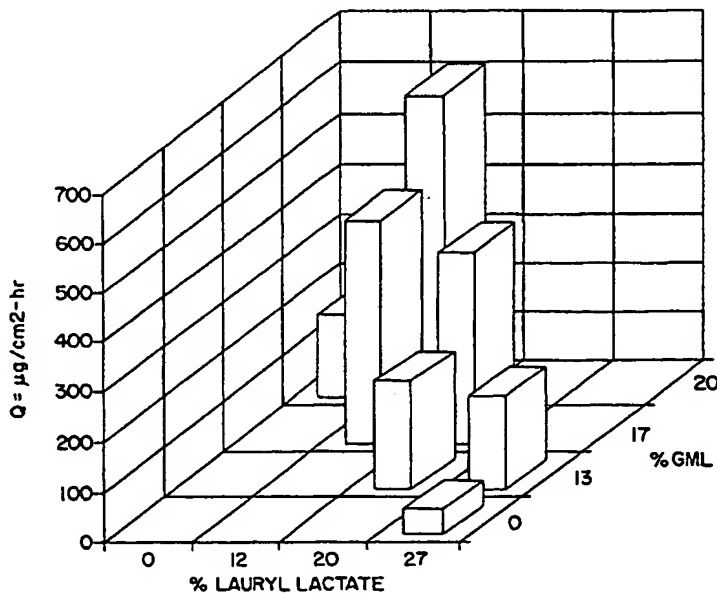




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : <b>A61K 47/14</b>		<b>A1</b>	(11) International Publication Number: <b>WO 95/09006</b>
			(43) International Publication Date: <b>6 April 1995 (06.04.95)</b>
(21) International Application Number: <b>PCT/US94/11120</b>		(74) Agents: <b>HARBIN, Alisa, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</b>	
(22) International Filing Date: <b>29 September 1994 (29.09.94)</b>			
(30) Priority Data: <b>129,494 29 September 1993 (29.09.93) US</b>		(81) Designated States: <b>AU, CA, FI, JP, KR, NO, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</b>	
(60) Parent Application or Grant (63) Related by Continuation <b>US 129,494 (CIP)</b> <b>Filed on 29 September 1993 (29.09.93)</b>		<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicant (for all designated States except US): <b>ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</b>			
(72) Inventors; and (75) Inventors/Applicants (for US only): <b>TASKOVICH, Lina, Tormen [EC/US]; 751 Gailen Avenue, Palo Alto, CA 94303 (US). YUM, Su, II [US/US]; 1021 Rummymead Court, Los Altos, CA 94021 (US). LEE, Eun, Soo [US/US]; 108 West Danbury, Redwood City, CA 94061 (US). CRISOLOGO, Nieves, Marzan [US/US]; 787 Madron Avenue, Sunnyvale, CA 94086 (US).</b>			

(54) Title: **MONOGLYCERIDE/LACTATE ESTER PERMEATION ENHANCER**

## (57) Abstract

A composition of matter for application to a body surface or membrane to administer a drug by permeation through the body surface or membrane, the composition comprising, in combination, the drug to be administered, in a therapeutically effective amount; and a permeation-enhancing mixture comprising a monoglyceride or a mixture of monoglycerides, and a lactate ester or a mixture of lactate esters.

## REFERENCE: CP

William VAN OSDOL et al., USSN: 10/675,715  
Atty. Docket No.: AR02817USACON

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

## MONOGLYCERIDE/LACTATE ESTER PERMEATION ENHANCER

### RELATED APPLICATIONS

This is a continuation-in-part of US application Serial No. 08/129,494, filed September 29, 1993, which application is incorporated herein in its entirety by reference and benefit is claimed of its filing date.

### FIELD OF THE INVENTION

This invention relates to the transdermal delivery of drugs and other biologically active agents. More particularly, this invention relates to novel methods and compositions for enhancing the percutaneous absorption of  
5 drugs when incorporated in transdermal drug delivery systems. More particularly, but without limitation thereto, this invention relates to the transdermal delivery of drugs utilizing a permeation-enhancing mixture of a monoglyceride and a lactate ester. Still more particularly, but without  
10 limitation thereto, this invention relates to the transdermal delivery of drugs utilizing a permeation-enhancing mixture of a monoglyceride and a lactate ester wherein the monoglyceride and lactate ester are present in the composition in specific weight percentages.

### BACKGROUND OF THE INVENTION

The transdermal route of parenteral delivery of drugs provides many  
15 advantages over other administrative routes, and transdermal systems for delivering a wide variety of drugs or other beneficial agents are described in US Patent Numbers 3,598,122; 3,598,123; 3,731,683; 3,797,494; 4,031,894; 4,201,211; 4,286,592; 4,314,557; 4,379,454; 4,435,180; 4,559,222; 4,568,343; 4,573,995; 4,588,580; 4,645,502; 4,704,282; 4,788,062;

4,816,258; 4,849,226; 4,908,027; 4,943,435; and 5,004,610. The disclosures of the above patents are incorporated herein by reference.

In many instances, drugs which would appear to be ideal candidates for transdermal delivery are found to have such low permeability through intact skin that they cannot be delivered at therapeutically effective rates from reasonably sized systems.

In an effort to increase skin permeability, it has been proposed to pretreat the skin with various chemicals or to concurrently deliver the drug in the presence of a permeation enhancer. Various materials have been suggested for this purpose, as described in US Pat. Nos. 3,472,931, 3,527,864, 3,896,238, 3,903,256, 3,952,099, 4,046,886, 4,130,643, 4,130,667, 4,299,826, 4,335,115, 4,343,798, 4,379,454, 4,405,616 and 4,746,515, all of which are incorporated herein by reference; British Pat. No. 1,001,949; and Idson, Percutaneous Absorption, J. Pharm. Sci., vol. 64, No. b6, June 1975, pp 901-924 (particularly 919-921).

To be considered useful, a permeation enhancer should have the ability to enhance the permeability of the skin for at least one and preferably a significant number of drugs. More importantly, it should be able to enhance the skin permeability such that the drug delivery rate from a reasonably sized system (preferably 5-50 cm<sup>2</sup>) is at therapeutic levels. Additionally, the enhancer, when applied to the skin surface, should be non-toxic, non-irritating on prolonged exposure and under occlusion, and non-sensitizing on repeated exposure. Preferably, it should be capable of delivering drugs without producing topical reactions, burning or tingling sensations.

The present invention greatly increases drug permeability through the skin, and also reduces the lag time between application of the drug to the skin and attainment of the desired therapeutic effect.

While it is known in the art to combine permeation enhancers, see,  
5 eg, European Patent Publication numbers 0295411 and 0368339, this invention utilizes a novel combination of a monoglyceride and a lactate ester. Further, the invention utilizes specific weight percentages of the novel components, the monoglyceride and lactate ester, ie, 15 to 25 wt% of monoglyceride and 8 to 25 wt% of lactic acid ester. The combined effect  
10 and, further, specific weight percentages, produces a significant and surprising improvement ie, more than an additive effect over use of either a monoglyceride or a lactate ester alone, as well as over the combination of monoglyceride and lactate ester in specified weight percentages.

#### SUMMARY OF THE INVENTION

15 The present invention relates to improved compositions and methods for improving the penetration of a broad category of beneficial agents that produce little or no skin irritation. The system of the invention comprises a carrier or matrix adapted to be placed in drug- and permeation-enhancing mixture-transmitting relation to the selected skin or other body site. The  
20 carrier or matrix contains sufficient amounts of drug and the permeation-enhancing mixture to continuously coadminister to the site, over a predetermined delivery period, the drug, in a therapeutically effective amount, and the permeation-enhancing mixture of a monoglyceride and a lactate ester, present in specific concentrations, ie, 15 to 25 wt% of  
25 monoglyceride and 8 to 25 wt% of a lactate ester, preferably 20 wt% monoglyceride and 12 wt% lactate ester in an amount effective to enhance the permeation of the drug to the skin.

As used herein, the term "transdermal" delivery or application refers to the delivery or application of agents by passage through skin, mucosa and/or other body surfaces by topical application or by iontophoresis.

As used herein, the term "therapeutically effective" amount or rate  
5 refers to the amount or rate of drug or active agent needed to effect the desired therapeutic result.

As used herein, the term "monoglyceride" refers to glycerol monooleate, glycerol monolaurate and glycerol monolinoleate, or a mixture thereof. Monoglycerides are generally available as a mixture of  
10 monoglycerides, with the mixture deriving its name from the monoglyceride present in the greatest amount. In a preferred embodiment of this invention, the permeation enhancer monoglyceride component is glycerol monolaurate.

As used herein, the term "glycerol monooleate" refers to glycerol monooleate itself or a mixture of glycerides wherein glycerol monooleate is  
15 present in the greatest amount.

As used herein, the term "glycerol monolaurate" refers to glycerol monolaurate itself or a mixture of glycerides wherein glycerol monolaurate is present in the greatest amount.

As used herein, the term "glycerol monolinoleate" refers to glycerol  
20 monolinoleate itself or a mixture of glycerides wherein glycerol monolinoleate is present in the greatest amount.

As used herein, the term "lactate ester" or "lactic ester of an alcohol" refers to ethyl lactate, lauryl lactate, myristyl lactate or cetyl lactate, or a mixture thereof. Preferably, the lactate ester is lauryl lactate or ethyl lactate  
25 or a mixture thereof.

As used herein, the term "substantial portion of the time period" means at least about 60% of the time period, preferably at least about 90% of the time period. Correlatively, the term "substantially constant" means a variation of less than about  $\pm 20\%$ , preferably less than about  $\pm 10\%$ , over a substantial portion of the time period.

As used herein, the term "permeation enhancing mixture" refers to a mixture comprising one or more lactate esters and one or more monoglycerides. The monoglyceride or mixture, preferably, glycerol monolaurate, is present in the range of about 15 to about 25 weight percent. The second component, ie, a lactic acid ester, eg, lauryl, myristyl, cetyl, ethyl, methyl or oleic acid, benzoic acid or lactic acid is present in the range of about 8 to about 25 weight percent. More preferably, the permeation enhancer mixture by weight comprises 20% monoglyceride and 12% lactic acid ester.

As used herein, the term "predetermined delivery period" or "extended time period" refers to the delivery of drug for a time period of from several hours to seven days or longer. Preferably, the time period is from 16 hours to 3 or 4 days.

As used herein, the term "permeation enhancing amount or rate" refers to the rate or amount that provides increased permeability of the application site to the drug.

As used herein, the term "poly-N-vinyl amide" means a cross-linked poly-N-vinyl amide or combination of poly-N-vinyl amide such as poly-N-vinylmethylacetamide, poly-N-vinylethylacetamide, poly-N-vinylmethylisobutyramide, poly-N-vinyl-2-pyrrolidone, poly-N-vinylpyrrolidone, poly-N-vinyl-2-piperidone, poly-N-vinyl-caprolactam, poly-N-vinyl-5-methyl-2-pyrrolidone, poly-N-vinyl-3-methyl-2-pyrrolidone, and

the like. Preferably, the poly-N-vinyl amide is poly-N-vinyl-2-pyrrolidone (more preferably Polyplasdone XL®, Polyplasdone XL-10®, GAF).

#### BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described in further detail with reference to the  
5 accompanying drawings wherein:

FIG. 1 is a cross-sectional view of one embodiment of the transdermal drug delivery system according to this invention;

FIG. 2 is a cross-sectional view of another embodiment of the transdermal drug delivery system of this invention;

10 FIG. 3 is a cross-sectional view of still another embodiment of the transdermal drug delivery system according to this invention;

FIG. 4 is a cross-sectional view of yet another embodiment of the transdermal drug delivery system of this invention;

15 FIG. 5 is a graph of the flux of alprazolam through human epidermis at 35°C, in vitro, with glycerol monolaurate and lauryl lactate.

FIG. 6 is a graph of the flux of alprazolam through human epidermis at 35°C, in vitro, with glycerol monolaurate and lauryl lactate.

FIG. 7 is a graph of the flux of estradiol through human epidermis at 35°C, in vitro, with glycerol monolaurate and lauryl lactate.

20 FIG. 8 is a graph of the flux of testosterone through human epidermis at 35°C, in vitro, with glycerol monolaurate and lauryl lactate.



FIG. 9 is a bar graph of the cumulative flux of alprazolam through human epidermis at 35°C, in vitro, with varying weight percents of glycerol monolaurate and lauryl lactate.

FIG. 10 is a graph of the cumulative flux of testosterone through  
5 human epidermis at 35°C, in vitro, with various flux enhancers.

FIG. 11 is a bar graph showing the effect of various concentrations of glycerol monolaurate and lauryl lactate on the flux of alprazolam through human epidermis at 35°C, in vitro.

#### DESCRIPTION OF THE INVENTION

10 This invention co-delivers one or more monoglycerides and one or more lactate esters to aid in delivery of drugs across the skin. In addition, thereto this invention calls for the monoglycerides and lactate esters to be present in a specific concentrations eg, 15-25 wt% and 8-25 wt%, respectively. The combined effect and preferred concentrations according to  
15 this invention have been shown to produce dramatic, ie, more than an additive, increases in the permeation of drugs when compared to the use of either a lactate ester or a monoglyceride alone or in unspecified weight percentages. Improved enhancement of permeation according to this invention can be obtained over a relatively wide range of lactate  
20 ester/monoglyceride weight percentages given above, however, the inventors have found that 20 wt% and 12 wt% of the monoglyceride and lactate ester, respectively, provides the greatest enhancement without any negative side effect.

The present invention in one embodiment is directed to a composition  
25 of matter for application to a body surface or membrane to administer a drug

by permeation through the body surface or membrane, the composition comprising, in combination:

- (a) the drug to be administered, in a therapeutically effective amount; and
- 5 (b) a permeation-enhancing mixture comprising:
  - (i) 15 to 25 wt% of a monoglyceride or a mixture of monoglycerides, and
  - (ii) 8 to 25 wt% of a lactate ester or a mixture of lactate esters.

10 The drug may be present in the composition in an amount ranging from 0.01 to 50% by weight. The permeation-enhancing mixture preferably contains the monoglyceride and lactate ester in 20 wt% and 12 wt%, respectively.

This invention finds particular usefulness in enhancing drug  
15 permeability across skin. It is also useful, however, in enhancing flux across mucosa. Further, this invention is useful in delivery of both systemically and topically active drugs. According to our invention, the permeation-enhancing mixture and the drug to be delivered are placed in drug- and permeation-enhancing mixture-transmitting relationship to the appropriate body surface,  
20 preferably in a pharmaceutically acceptable carrier therefor, and maintained in place for the desired period of time.

The drug and the permeation-enhancing mixture are typically dispersed within a physiologically compatible matrix or carrier as more fully described below which may be applied directly to the body as an ointment,  
25 gel, cream, suppository or sublingual or buccal tablet, for example. When used in the form of a liquid, ointment, lotion, cream or gel applied directly to the skin, it is preferable, although not required, to occlude the site of administration. Such compositions can also contain other permeation

enhancers, stabilizers, dyes, diluents, pigments, vehicles, inert fillers, excipients, gelling agents, vasoconstrictors, and other components of topical compositions as are known to the art.

In other embodiments, the drug and permeation enhancing mixture  
5 would be administered from a transdermal delivery device as more fully described below. Examples of suitable transdermal delivery devices are illustrated in Figures 1, 2, 3 and 4. In the drawings, the same reference numbers are used throughout the different figures to designate the same or similar components. The figures are not drawn to scale.

10 In Figure 1, transdermal delivery device 10 comprises a reservoir 12 containing the drug and the permeation-enhancing mixture. Reservoir 12 is preferably in the form of a matrix containing the drug and permeation enhancing mixture dispersed therein. Reservoir 12 is sandwiched between a backing layer 14 and an in-line contact adhesive layer 16. The device 10  
15 adheres to the surface of the skin 18 by means of the adhesive layer 16. The adhesive layer 16 may optionally contain the permeation enhancing mixture and/or drug. A strippable release liner (not shown in Figure 1) is normally provided along the exposed surface of adhesive layer 16 and is removed prior to application of device 10 to the skin 18. Optionally, a rate-  
20 controlling membrane (not shown) may be present between the reservoir 12 and the adhesive layer 16.

Alternatively, as shown in Figure 2, transdermal therapeutic device 20  
may be attached to the skin or mucosa of a patient by means of an adhesive overlay 22. Device 20 is comprised of a drug- and permeation enhancing  
25 mixture-containing reservoir 12 which is preferably in the form of a matrix containing the drug and the enhancing mixture dispersed therein. A backing layer 14 is provided adjacent one surface of reservoir 12. Adhesive overlay 22 maintains the device on the skin and may be fabricated together with, or

provided separately from, the remaining elements of the device. With certain formulations, the adhesive overlay 22 may be preferable to the in-line contact adhesive 16 as shown in Figure 1. Backing layer 14 is preferably slightly larger than reservoir 12, and in this manner prevents the materials in reservoir 12 from adversely interacting with the adhesive in overlay 22. 5 Optionally, a rate-controlling membrane (not shown in Figure 2) may be provided on the skin-proximal side of reservoir 12. A strippable release liner 24 is also provided with device 20 and is removed just prior to application of device 20 to the skin.

10 In Figure 3, transdermal delivery device 30 comprises a drug- and permeation enhancing mixture-containing reservoir ("drug reservoir") 12 substantially as described with respect to Figure 1. Permeation enhancer reservoir ("enhancer reservoir") 26 comprises the permeation enhancing mixture dispersed throughout and the drug at or below saturation when in 15 equilibrium. Enhancer reservoir 26 is preferably made from substantially the same matrix as is used to form drug reservoir 12. A rate-controlling membrane 28 for controlling the release rate of the permeation enhancer from enhancer reservoir 26 to drug reservoir 12 is placed between the two reservoirs. A rate-controlling membrane (not shown in Figure 3) for 20 controlling the release rate of the enhancer from drug reservoir 12 to the skin may also optionally be utilized and would be present between adhesive layer 16 and reservoir 12.

The rate-controlling membrane may be fabricated from permeable, semipermeable or microporous materials which are known in the art to 25 control the rate of agents into and out of delivery devices and having a permeability to the permeation enhancer lower than that of drug reservoir 12. Suitable materials include, but are not limited to, polyethylene, polyvinyl acetate, ethylene n-butyl acetate and ethylene vinyl acetate copolymers.

Superimposed over the permeation enhancer reservoir 26 of device 30 is a backing 14. On the skin-proximal side of reservoir 12 are an adhesive layer 16 and a strippable liner 24 which would be removed prior to application of the device 30 to the skin.

5 In the embodiments of Figures 1, 2 and 3, the carrier or matrix material of the reservoirs has sufficient viscosity to maintain its shape without oozing or flowing. If, however, the matrix or carrier is a low-viscosity flowable material such as a liquid or a gel, the composition can be fully enclosed in a pouch or pocket, as known to the art from US Pat. No.  
10 4,379,454 (noted above), for example, and as illustrated in Figure 4. Device 40 shown in Figure 4 comprises a backing member 14 which serves as a protective cover for the device, imparts structural support, and substantially keeps components in device 40 from escaping the device. Device 40 also includes reservoir 12 which contains the drug and permeation enhancing  
15 mixture and bears on its surface distant from backing member 14 a rate-controlling membrane 28 for controlling the release of drug and/or permeation enhancing mixture from device 40. The outer edges of backing member 14 overlay the edges of reservoir 12 and are joined along the perimeter with the outer edges of the rate-controlling membrane 28 in a fluid-  
20 tight arrangement. This sealed reservoir may be effected by pressure, fusion, adhesion, an adhesive applied to the edges, or other methods known in the art. In this manner, reservoir 12 is contained wholly between backing member 14 and rate-controlling membrane 28. On the skin-proximal side of rate-controlling membrane 28 are an adhesive layer 16 and a strippable  
25 liner 24 which would be removed prior to application of the device 40 to the skin.

In an alternative embodiment of device 40 of Figure 4, reservoir 12 contains the permeation enhancing mixture and the drug at or below saturation. The drug at saturation and an additional amount of permeation

enhancing mixture are present in adhesive layer 16 which acts as a separate reservoir.

The drug and the permeation enhancing mixture can be co-extensively administered to human skin or mucosa by direct application to the skin or mucosa in the form of an ointment, gel, cream or lotion, for example, but are preferably administered from a skin patch or other known transdermal delivery device which contains a saturated or subsaturated formulation of the drug and the enhancer. The formulation is non-aqueous based and designed to deliver the drug and the permeation enhancing mixture at the necessary fluxes. Typical non-aqueous gels are comprised of silicone fluid or mineral oil. Mineral oil-based gels also typically contain 1-2 wt% of a gelling agent such as colloidal silicon dioxide. The suitability of a particular gel depends upon the compatibility of its constituents with both the drug and the permeation enhancing mixture and any other components in the formulation.

The reservoir matrix should be compatible with the drug, the permeation enhancer and any carrier therefor. The term "matrix" as used herein refers to a well-mixed composite of ingredients fixed into shape.

When using a non-aqueous-based formulation, the reservoir matrix is preferably composed of a hydrophobic polymer. Suitable polymeric matrices are well known in the transdermal drug delivery art, and examples are listed in the above-named patents previously incorporated herein by reference. A typical laminated system would comprise a polymeric membrane and/or matrix such as ethylene vinyl acetate (EVA) copolymers, such as those described in US Pat. No. 4,144,317, preferably having a vinyl acetate (VA) content in the range of from about 9% up to about 60% and more preferably about 9% to 40% VA. Polyisobutylene/oil polymers containing from 4-25% high molecular weight polyisobutylene and 20-81% low molecular weight

polyisobutylene with the balance being an oil such as mineral oil or polyisobutylenes may also be used as the matrix material.

The amount of drug present in the therapeutic device and required to achieve an effective therapeutic result depends on many factors, such as the  
5 minimum necessary dosage of the drug for the particular indication being treated; the solubility and permeability of the matrix, of the adhesive layer and of the rate-controlling membrane, if present; and the period of time for which the device will be fixed to the skin. The minimum amount of drug is determined by the requirement that sufficient quantities of drug must be  
10 present in the device to maintain the desired rate of release over the given period of application. The maximum amount for safety purposes is determined by the requirement that the quantity of drug present cannot exceed a rate of release that reaches toxic levels.

The drug is normally present in the matrix or carrier at a concentration  
15 in excess of saturation, the amount of excess being a function of the desired length of the drug delivery period of the system. The drug may, however, be present at a level below saturation without departing from this invention as long as the drug is continuously administered to the skin or mucosal site in an amount and for a period of time sufficient to provide the desired  
20 therapeutic rate.

The permeation enhancing mixture is dispersed through the matrix or carrier, preferably at a concentration sufficient to provide permeation-enhancing amounts of enhancer in the reservoir throughout the anticipated administration period. Where there is an additional, separate permeation  
25 enhancer matrix layer as well, as in Figures 3 and 4, the permeation enhancer normally is present in the separate reservoir in excess of saturation.

The unexpected effects of the specific weight percentages of the components of the permeation enhancer mixture is due, in part to the solubility of the monoglyceride in the lactic acid ester. It is known that monoglycerides by themselves are effective permeation enhancers. The enhancement occurs by the solubilization of the monoglyceride in the lipid layer of the skin. The solubilization of the monoglyceride in the lipid layer increases as a function of lactic acid ester concentration. For example, the solubility of glycerol monolaurate in lauryl lactate is 350 mg/g of solution when the solution is stirred. GML is practically insoluble in, for example, an EVA 40 matrix. Thus, the amount of GML dissolved, ie, free GML is dictated by and proportional to the lauryl lactate loading in the polymer.

Based on the GML solubility of 350 mg/g, free GML concentrations based upon varying weight percents of lauryl lactate in EVA 40 are as follows:

<u>Wt% Lauryl Lactate</u>	<u>Wt% GML in Solution</u>
12%	4.2%
20%	7.0%
27%	9.5%
30%	10.5%

Thus, based upon the amount of GML in solution it would have appeared that the higher wt% of lauryl lactate would have resulted in a higher level of free GML and thus greater efficacy in increasing permeation. However, as shown by the examples, the preferred formulations, containing 20 wt% GML and 12 wt% lauryl lactate, were equally effective in enhancing drug permeability as those containing 20 wt% GML and 20 wt% lauryl lactate. While the invention is directed to a permeation enhancing mixture containing a monoglyceride or monoglyceride mixture from 15 to 25 wt% and a lactic acid ester present from 8 to 25 wt%, the 20 wt% monoglyceride and 12 wt% lactic acid ester is preferred because it is as effective as the higher



percentage lactic acid ester compositions yet it delivers less of a lactic acid ester which is a known potential irritant.

In addition to drug and the permeation enhancing mixture, which are essential to the invention, the matrix or carrier may also contain dyes,  
5 pigments, inert fillers, excipients and other conventional components of pharmaceutical products or transdermal devices known to the art.

Because of the wide variation in skin permeability from individual to individual and from site to site on the same body, it may be preferable that drug and the permeation enhancing mixture be administered from a  
10 rate-controlled transdermal delivery device. Rate control can be obtained either through a rate-controlling membrane or adhesive or both as well as through the other means.

A certain amount of drug will bind reversibly to the skin, and it is accordingly preferred that the skin-contacting layer of the device include this  
15 amount of the agent as a loading dose.

The surface area of the device of this invention can vary from less than 1 cm<sup>2</sup> to greater than 200 cm<sup>2</sup>. A typical device, however, will have a surface area within the range of about 5-50 cm<sup>2</sup>.

The devices of this invention can be designed to effectively deliver  
20 drug for an extended time period of from several hours up to 7 days or longer. Seven days is generally the maximum time limit for application of a single device because the adverse affect of occlusion of a skin site increases with time and the normal cycle of sloughing and replacement of the skin cells occurs in about 7 days.

25 The method of this invention comprises:

(a) administering a drug, in a therapeutically effective amount, to the area of skin over the time period; and

(b) coadministering the permeation-enhancing mixture according to this invention to the area of skin.

5           The composition delivered by the method contains a permeation enhancing mixture, ie, 15 to 25 wt% or a monoglyceride or monoglyceride mixture and 8 to 25 wt% of a lactate ester and enough drug to provide systemic administration of drug through the skin for a predetermined period of time to provide an effective therapeutic result.

10           It is believed that this invention has utility in connection with the delivery of drugs within the broad class normally delivered through body surfaces and membranes, including skin. As used herein, the expressions "drug" and "agent" are used interchangeably and are intended to have their broadest interpretation as to any therapeutically active substance which is  
15           delivered to a living organism to produce a desired, usually beneficial, effect. In general, this includes therapeutic agents in all of the major therapeutic areas, including, but not limited to, ACE inhibitors, adenohipophyseal hormones, adrenergic neuron blocking agents, adrenocortical steroids, inhibitors of the biosynthesis of adrenocortical steroids, alpha-adrenergic  
20           agonists, alpha-adrenergic antagonists, selective alpha-two-adrenergic agonists, analgesics, antipyretics and anti-inflammatory agents, androgens, local anesthetics, general anesthetics, antiaddictive agents, antiandrogens, antiarrhythmic agents, antiasthmatic agents, anticholinergic agents, anticholinesterase agents, anticoagulants, antidiabetic agents, antidiarrheal  
25           agents, antidiuretic, antiemetic and prokinetic agents, antiepileptic agents, antiestrogens, antifungal agents, antihypertensive agents, antimicrobial agents, antimigraine agents, antimuscarinic agents, antineoplastic agents, antiparasitic agents, antiparkinson's agents, antiplatelet agents, antiprogestins, antithyroid agents, antitussives, antiviral agents, atypical

antidepressants, azaspirodecanediones, barbiturates, benzodiazepines, benzothiadiazides, beta-adrenergic agonists, beta-adrenergic antagonists, selective beta-one-adrenergic antagonists, selective beta-two-adrenergic agonists, bile salts, agents affecting volume and composition of body fluids, butyrophenones, agents affecting calcification, calcium channel blockers, cardiovascular drugs, catecholamines and sympathomimetic drugs, cholinergic agonists, cholinesterase reactivators, dermatological agents, diphenylbutylpiperidines, diuretics, ergot alkaloids, estrogens, ganglionic blocking agents, ganglionic stimulating agents, hydantoins, agents for control of gastric acidity and treatment of peptic ulcers, hematopoietic agents, histamines, histamine antagonists, 5-hydroxytryptamine antagonists, drugs for the treatment of hyperlipoproteinemia, hypnotics and sedatives, immunosuppressive agents, laxatives, methylxanthines, monoamine oxidase inhibitors, neuromuscular blocking agents, organic nitrates, opioid analgesics and antagonists, pancreatic enzymes, phenothiazines, progestins, prostaglandins, agents for the treatment of psychiatric disorders, retinoids, sodium channel blockers, agents for spasticity and acute muscle spasms, succinimides, thioxanthenes, thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of tubular transport of organic compounds, drugs affecting uterine motility, vasodilators, vitamins and the like.

Representative drugs include, by way of example and not for purposes of limitation, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nitredipine, verapamil, dobutamine, isoproterenol, carteolol, labetalol, levobunolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol, acebutolol, atenolol, betaxolol, esmolol, metoprolol, albuterol, bitolterol, isoetharine, metaproterenol, pirbuterol, ritodrine, terbutaline, alclometasone, aldosterone, amcinonide, beclomethasone dipropionate, betamethasone, clobetasol, clocortolone, cortisol, cortisone, corticosterone, desonide, desoximetasone, 11-desoxycorticosterone, 11-desoxycortisol, dexamethasone, diflorasone, fludrocortisone, flunisolide, fluocinolone,

fluocinonide, fluorometholone, flurandrenolide, halcinonide, hydrocortisone, medrysone, 6 $\alpha$ -methylprednisolone, mometasone, paramethasone, prednisolone, prednisone, tetrahydrocortisol, triamcinolone, benoxinate, benzocaine, bupivacaine, chloroprocaine, cocaine, dibucaine, dyclonine, etidocaine, lidocaine, mepivacaine, pramoxine, prilocaine, procaine, proparacaine, tetracaine, alfentanil, chloroform, clonidine, cyclopropane, desflurane, diethyl ether, droperidol, enflurane, etomidate, fentanyl, halothane, isoflurane, ketamine hydrochloride, meperidine, methohexital, methoxyflurane, morphine, propofol, sevoflurane, sufentanil, thiamylal, thiopental, acetaminophen, allopurinol, apazone, aspirin, auranofin, aurothioglucose, colchicine, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, gold sodium thiomalate, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, mesalamine, methyl salicylate, nabumetone, naproxen, oxyphenbutazone, phenacetin, phenylbutazone, piroxicam, salicylamide, salicylate, salicylic acid, salsalate, sulfasalazine, sulindac, tolmetin, acetophenazine, chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine, triflupromazine, disopyramide, encainide, flecainide, indecainide, mexiletine, moricizine, phenytoin, procainamide, propafenone, quinidine, tocainide, cisapride, domperidone, dronabinol, haloperidol, metoclopramide, nabilone, prochlorperazine, promethazine, thiethylperazine, trimethobenzamide, buprenorphine, butorphanol, codeine, dezocine, diphenoxylate, drocode, hydrocodone, hydromorphone, levallorphan, levorphanol, loperamide, meptazinol, methadone, nalbuphine, nalmefene, nalorphine, naloxone, naltrexone, oxycodone, oxymorphone, pentazocine, propoxyphene, isosorbide dinitrate, nitroglycerin, theophylline, phenylephrine, ephedrine, pilocarpine, furosemide, tetracycline, chlorpheniramine, ketorolac, bromocriptine, guanabenz, prazosin, doxazosin, and flufenamic acid.

Preferably, the drug is a benzodiazepine, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate,

demoxepam, diazepam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, triazolam, and the like; an antimuscarinic agents, such as anisotropine, atropine, clidinium, cyclopentolate, dicyclomine, flavoxate, glycopyrrolate, hexocyclium, homatropine, ipratropium, isopropamide, mepenzolate, methantheline, oxyphencyclimine, pirenzepine, propantheline, scopolamine, telenzepine, tridihexethyl, tropicamide, and the like; an estrogen such as chlorotrianisene, diethylstilbestrol, estradiol, estradiol cypionate, estradiol valerate, estrone, estrone sodium sulfate, estropipate, ethinyl estradiol, mestranol, quinestrol, sodium equilin sulfate and the like; an androgen, such as danazol, fluoxymesterone, methandrostenolone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol, testolactone, testosterone, testosterone cypionate, testosterone enanthate, testosterone propionate, and the like; or a progestin such as ethynodiol diacetate, gestodene, hydroxyprogesterone caproate, levonorgestrel, medroxyprogesterone acetate, megestrol acetate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, progesterone, and the like.

Preferably, a device for the transdermal administration of a drug, at a therapeutically effective rate, comprises:

- (a) a reservoir comprising:
  - (i) a therapeutically effective amount of a drug or active agent,
  - (ii) 15 to 25% by weight monoglyceride or mixture of monoglycerides,
  - (iii) 8 to 25% by weight lactic acid ester, and
  - (iv) the remainder ethylene vinyl acetate copolymer;
- (b) a backing on the skin-distal surface of the reservoir; and
- (c) means for maintaining the reservoir in drug- and permeation enhancing mixture-transmitting relation with the skin.

Preferably, the monoglyceride is glycerol monolaurate and the lactic acid ester is lauryl lactate.

More preferably, a device for the transdermal administration of the drug, at a therapeutically effective rate, comprises:

- 5 (a) a reservoir comprising:
  - (i) 5 to 40% by weight drug,
  - (ii) 20% by weight glycerol monolaurate,
  - (iii) 12% by weight lauryl lactate, and
  - (iv) 28 to 63% by weight ethylene vinyl acetate copolymer;
- 10 (b) a backing on the skin-distal surface of the reservoir; and
- (c) means for maintaining the reservoir in drug- and permeation enhancing mixture-transmitting relation with the skin.

In one embodiment, the reservoir further comprises 5-25% by weight cross-linked poly-N-vinyl-2-pyrrolidone, eg, N-vinyl-2-pyrrolidone XL-10, G&F). Preferably, the backing is a breathable backing, such as NRU-100-C® (Flexcon, Spencer, MA). If an occluded backing is used, preferably it is Medpar® (3M, St. Paul, MN). Preferably, the means for maintaining the reservoir in drug and permeation enhancing mixture transmitting relation with the skin is an acrylic contact adhesive, such as MSP041991P, 3M.

20 Preferably, the ethylene vinyl acetate copolymer has a acetate content of 33% or 40%.

The aforementioned patents describe a wide variety of materials which can be used for fabricating the various layers or components of the transdermal drug delivery devices according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions. The following

25

examples are offered to illustrate the practice of the present invention and are not intended to limit the invention in any manner.

### EXAMPLE 1

The drug/permeation enhancer reservoir was prepared by mixing  
5 ethylene vinyl acetate copolymer having a vinyl acetate content of 40  
percent ("EVA 40", U.S.I. Chemicals, Illinois) in an internal mixer (Bra  
Bender type mixer) until the EVA 40 pellets fused. Alprazolam (GYMA Labs  
of America, Garden City, NJ), glycerol monolaurate (Grindsted ML 90,  
Grindsted Products A/S, Brabrand, Denmark) and lauryl lactate (Van  
10 Dyk, Inc., Bellevue, NJ) were then added. The mixture was blended for  
approximately 20 minutes at 54°-56°C and 30 rpm. After blending, the  
mixture was quickly cooled to 40°-45°C, and calendered to a 13 mil thick  
film. The film was then laminated to an acrylic contact adhesive  
(MSPO419910, 3M) on one side and a Medpar® backing (3M, St. Paul,  
15 Minn.) or NRU-100-C® backing (Flexcon, Spencer, MA) on the opposite  
side. The laminate was then cut into circles using a stainless steel punch.

The composition of the drug reservoirs is shown in Table 1.

TABLE 1

Drug/Permeation Enhancer Reservoir Composition (weight percent)	
Figure 5	
5	alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 (15/20/20/45)
	alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 (15/10/30/45)
10	alprazolam/lauryl lactate/EVA 40 (15/30/55)
Figure 6	
	alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 (15/20/20/45)
15	alprazolam/glycerol monolaurate/EVA 40 (15/20/65)

Circular pieces of human-epidermis were mounted on horizontal permeation cells with the stratum corneum facing the donor compartment of the cell. The release liner of the system was then removed and the system was centered over the stratum corneum side of the epidermis. A known volume of the receptor solution (0.01 M potassium phosphate at pH 6 containing 2% isopropanol) that had been equilibrated at 35°C was placed in the receptor compartment. Air bubbles were removed from the receptor compartment; the cell was capped and placed in a water bath-shaker at 35°C.

At given time intervals, the entire receptor solution was removed from the cells and replaced with an equal volume of fresh receptor solutions previously equilibrated at 35°C. The receptor solutions were stored in capped vials at 4°C until assayed for alprazolam content by HPLC. From the drug concentration and the volume of the receptor solutions, the area of



permeation and the time interval, the flux of the drug through the epidermis was calculated as follows: (drug concentration x volume of receptor)/(area x time) = flux ( $\mu\text{g}/\text{cm}^2\cdot\text{hr}$ ). The fluxes achieved for the different systems are shown in Figures 5 and 6. As can be seen in Figures 5 and 6, the fluxes  
5 obtained from the systems containing glycerol monolaurate and lauryl lactate were significantly higher than the fluxes obtained from the systems containing either glycerol monolaurate or lauryl lactate.

## EXAMPLE 2

The drug/permeation enhancer reservoir was prepared by mixing  
10 ethylene vinyl acetate copolymer having a vinyl acetate content of 40 percent ("EVA 40", U.S.I. Chemicals, Illinois) in an internal mixer (Bra Bender type mixer) until the EVA 40 pellets fused. Alprazolam, glycerol monolaurate and lauryl lactate were then added. The mixture was blended for approximately 20 minutes at 54°-56°C and 30 rpm. After blending, the  
15 mixture was quickly cooled to 40°-45°C, and calendered to a 5 mil thick film. The compositions of reservoirs are shown in Table 2.

TABLE 2

Composition of Reservoir	Plasma Levels of Alprazolam (ng/mL)	
	24 hrs	48 hrs
alprazolam/glycerol monolaurate/ EVA 40 (15%/20%/65%)	0.2	0.2
alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 (15%/20%/20%/45%)	0.7	1.2

This film was then laminated to an acrylic contact adhesive (MSP041991P, 3M) on one side and Medpar® backing (3M) on the opposite side. The laminate was then cut into 5 cm<sup>2</sup> square. As can be seen in Table 3, the plasma levels for the combination of glycerol monolaurate and lauryl lactate was significantly higher than the plasma level for glycerol monolaurate alone.

### EXAMPLE 3

The drug/permeation enhancer reservoir was prepared by mixing ethylene vinyl acetate copolymer having a vinyl acetate content of 28 percent ("EVA 28", U.S.I. Chemicals, Illinois) and cross-linked poly-N-vinyl-2-pyrrolidone (Polyplasdone XL-10®, GAF) in an internal mixer (Bra Bender type mixer) until the EVA 28 pellets fused. Estradiol, glycerol monolaurate and lauryl lactate were then added. The mixture was blended, and calendered to a 4.0 mil thick film. The compositions of the reservoir is given in Table 3.

TABLE 3

Drug/Permeation Enhancer Reservoir Composition (weight percent)	
Estradiol/glycerol monolaurate/lauryl lactate/EVA 28/N-vinyl-2-pyrrolidone (2.5/20/20/52.5/5)	

This film was then laminated to an acrylic contact adhesive (147-123-4, Adhesive Research Co.) on one side and dermaFlex NRU-100-C® backing (Flexcon Co.) on the opposite side. The film was then cut into circles and taped to prevent edge release.

For each device tested, the adhesive was placed against the stratum corneum side of a disc of human epidermis that had been blotted dry just prior to use. The excess epidermis was wrapped around the device so that none of the device edge was exposed to the receptor solution. The device  
5 covered with epidermis was attached to the flat side of the Teflon holder of a release rod using nylon netting and nickel wire. The rods were reciprocated in a fixed volume of receptor solution (distilled water). The entire receptor solution was changed at each sampling time. The temperature of the receptor solution in the water bath was maintained at 35°C.

10 The receptor solutions were stored in capped vials at 4°C until assayed for estradiol content by HPLC. The fluxes achieved for the different systems are shown in Figure 7.

#### EXAMPLE 4

The drug/permeation enhancer reservoir was prepared by mixing  
15 ethylene vinyl acetate copolymer having a vinyl acetate content of 28 percent ("EVA 28", U.S.I. Chemicals, Illinois) and cross-linked poly N-vinyl-2-pyrrolidone (Polyplasdone XL®, GAF) in an internal mixer (Bra Bender type mixer) until the EVA 28 pellets fused. Testosterone, glycerol monolaurate and lauryl lactate were then added. The mixture was blended,  
20 and calendered to a 4.0 mil thick film. The compositions of the reservoir is given in Table 4.

TABLE 4

Drug/Permeation Enhancer Reservoir Composition (weight percent)
testosterone/glycerol monolaurate/lauryl lactate/EVA 28/N-vinyl-2-pyrrolidone (5/20/20/50/5)

5

This film was then laminated to an acrylic contact adhesive (147-123-4, Adhesive Research Co.) on one side and dermaFlex NRU-100-C® backing (Flexcon Co.) on the opposite side. The film was then cut into circles and taped to prevent edge release.

10

For each device tested, the adhesive was placed against the stratum corneum side of a disc of human epidermis that had been blotted dry just prior to use. The excess epidermis was wrapped around the device so that none of the device edge was exposed to the receptor solution. The device covered with epidermis was attached to the flat side of the Teflon holder of a release rod using nylon netting and nickel wire. The rods were reciprocated in a fixed volume of receptor solution (distilled water). The entire receptor solution was changed at each sampling time. The temperature of the receptor solution in the water bath was maintained at 35°C.

15

The receptor solutions were stored in capped vials at 4°C until assayed for testosterone content by HPLC. The fluxes achieved for the different systems are shown in Figure 8.

20

#### EXAMPLE 5

The drug/permeation enhancer reservoir was prepared by mixing ethylene vinyl acetate copolymer having a vinyl acetate content of 40

25

percent ("EVA 40", U.S.I. Chemicals, Illinois) in an internal mixer (Bra  
Bender type mixer) until the EVA 40 pellets fused. Alprazolam, glycerol  
monolaurate and lauryl lactate were then added. The mixture was blended  
for approximately 20 minutes at 54°-56°C and 30 rpm. After blending, the  
5 mixture was quickly cooled to 40°-45°C, and calendared to a 5 mil thick film.  
The composition of the drug reservoirs is shown in Table 5.

TABLE 5

Drug/Permeation Enhancer Reservoir Composition (weight percent)
Figure 9
alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/20/0/65
alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/20/12/53
alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/17/12/56
alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/17/20/48
alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/13/20/52
alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/13/27/45
alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/0/27/58

25 This film was then laminated to an acrylic contact adhesive  
(MSP041991P, 3M) on one side and Medpar® or NRU-100-C® backing  
(Flexcon, Spencer, MA) on the opposite side. The laminate was then cut  
into circles using a stainless steel punch.

Circular pieces of human-epidermis were mounted on horizontal permeation cells with the stratum corneum facing the donor compartment of the cell. The release liner of the system was then removed and the system was centered over the stratum corneum side of the epidermis. A known  
5 volume of the receptor solution (0.01 M potassium phosphate at pH 6 containing 2% isopropanol) that had been equilibrated at 35°C was placed in the receptor compartment. Air bubbles were removed; the cell was capped and placed in a water bath-shaker at 35°C.

At given time intervals, the entire receptor solution was removed from  
10 the cells and replaced with an equal volume of fresh receptor solutions previously equilibrated at 35°C. The receptor solutions were stored in capped vials at 4°C until assayed for alprazolam content by HPLC. The fluxes achieved for the different systems are shown in Figure 9. As is demonstrated by Figure 9, a system containing 20% GML and 12% LL  
15 provided a superior cumulative flux of alprazolam.

#### EXAMPLE 6

The drug/permeation enhancer reservoir was prepared by mixing ethylene vinyl acetate copolymer having a vinyl acetate content of 40 percent ("EVA 40", U.S.I. Chemicals, Illinois) and optionally cross-linked poly  
20 N-vinyl- 2-pyrrolidone (Polyplasdone XL®, GAF) in an internal mixer (Bra Bender type mixer) until the EVA 40 pellets fused. Testosterone, glycerol monolaurate and lauryl lactate were then added. The mixture was blended, and calendered to a 4.0 mil thick film. The compositions of the reservoir is given in Table 6.

TABLE 6

Drug/Permeation Enhancer Reservoir Composition (weight percent)
5 testosterone/glycerol monolaurate/lauryl lactate/EVA 40 (5/20/20/50/5)
testosterone/glycerol monolaurate/myristyl lactate/myristyl alcohol/EVA 40 (20/20/12/48)
10 testosterone/glycerol monolaurate/lauric acid/EVA 40 (20/20/12/48)
testosterone/glycerol monolaurate/Tween 20/EVA 40 (20/20/10/50)
testosterone/glycerol monolaurate/lauryl lactate/EVA 40 (20/20/12/48)
15 testosterone/glycerol monolaurate/lauryl lactate/N-vinyl-2- pyrrolidone/EVA 40 (20/20/12/16/32)

This film was then laminated to an acrylic contact adhesive (MSP041991P, 3M) on one side and Medpar® or NRU-100-C® backing on the opposite side. The laminate was then cut into circles and taped to prevent edge release.

For each device tested, the adhesive was placed against the stratum corneum side of a disc of human epidermis that had been blotted dry just prior to use. The excess epidermis was wrapped around the device so that none of the device edge was exposed to the receptor solution. The device covered with epidermis was attached to the flat side of the Teflon holder of a release rod using nylon netting and nickel wire. The rods were reciprocated in a fixed volume of receptor solution (0.1% Benzoic acid). The entire

receptor solution was changed at each sampling time. The temperature of the receptor solution in the water bath was maintained at 35°C.

The receptor solutions were stored in capped vials at 4°C until assayed for testosterone content by HPLC. The fluxes achieved for the  
5 different systems are shown in Figure 10.

### EXAMPLE 7

The drug/permeation enhancer reservoir was prepared by mixing ethylene vinyl acetate copolymer having a vinyl acetate content of 40 percent ("EVA 40", U.S.I. Chemicals, Illinois) in an internal mixer (Bra  
10 Bender type mixer) until the EVA 40 pellets fused. Alprazolam, glycerol monolaurate and lauryl lactate were then added. The mixture was blended, and calendered to a 5.0 mil thick film. The composition of the reservoirs are given in Table 7.

TABLE 7

15	Drug/Permeation Enhancer Reservoir Composition (weight percent)
	Alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/10/30/45
20	Alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/20/20/45
	Alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/13/27/45
	Alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/20/12/53
25	Alprazolam/glycerol monolaurate/lauryl lactate/EVA 40 15/0/0/85



The film was then laminated to an acrylic contact adhesive (MSPO41991P, 3M) on one side and Medpar® or NRU-100-C® backing (Flexcon Co.) on the opposite side. The film was then cut into circles and taped to prevent drug release from the edges.

5           For each device tested, the adhesive was placed against the stratum corneum side of a disc of human epidermis that had been blotted dry just prior to use. The excess epidermis was wrapped around the device so that none of the device edge was exposed to the receptor solution. The device covered with epidermis was attached to the flat side of the Teflon holder of a  
10       release rod using nylon netting and nickel wire. The rods were reciprocated in a fixed volume of receptor solution (0.01M potassium phosphate at pH 6 containing 2% isopropanol). The entire receptor solution was changed at each sampling time. The temperature of the receptor solution in the water bath was maintained at 35°C.

15           The receptor solutions were stored in capped vials at 4°C until assayed for alprazolam content by HPLC. The fluxes achieved for the different systems are shown in Figure 11.

          This invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that  
20       variations and modifications can be effected within the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A composition of matter for application to a body surface or membrane to administer a drug by permeation through the body surface or membrane, the composition comprising, in combination:
  - (a) the drug to be administered, in a therapeutically effective amount; and
  - (b) a permeation-enhancing mixture comprising:
    - (i) 15 to 25% by weight of a monoglyceride or a mixture of monoglycerides, and
    - (ii) 8 to 25% by weight of a lactate ester or a mixture of lactate esters.
2. A composition according to claim 1 wherein the monoglyceride or mixture of monoglycerides comprises 20% by weight of the composition and the lactate ester or mixture of lactate esters comprises 12% by weight of the composition.
3. A composition according to claim 1 wherein the lactate ester is lauryl lactate.
4. A composition according to claim 1 wherein the lactate ester is ethyl lactate.
5. A composition according to claim 1 wherein the lactate ester is myristyl lactate.
6. A composition according to claim 1 wherein the lactate ester is cetyl lactate.

7. A composition according to claim 1 wherein the mixture of lactate esters is ethyl lactate and lauryl lactate.

8. A composition according to claim 3, 4, 5, 6, or 7 wherein the monoglyceride is glycerol monolaurate.

9. A composition according to claim 8 wherein the glycerol monolaurate comprises 20% by weight of the composition and the lactate ester comprises 12% by weight of the composition.

10. A composition according to claim 1 wherein the drug is selected from the group consisting of a benzodiazepine, an antimuscarinic agent, an adrenocortical steroid, an estrogen, an androgen, or a progestin.

11. A composition according to claim 10 wherein the adrenocortical steroid is selected from the group consisting of alclometasone, aldosterone, amcinonide, beclomethasone dipropionate, betamethasone, clobetasol, clocortolone, cortisol, cortisone, corticosterone, desonide, desoximetasone, 11-desoxycorticosterone, 11-desoxycortisol, dexamethasone, diflorasone, fludrocortisone, flunisolide, fluocinolone, fluocinonide, fluorometholone, flurandrenolide, halcinonide, hydrocortisone, medrysone, 6 $\alpha$ -methylprednisolone, mometasone, paramethasone, prednisolone, prednisone, tetrahydrocortisol or triamcinolone.

12. A composition according to claim 10 wherein the androgen is selected from the group consisting of danazol, fluoxymesterone, methandrostenolone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol, testolactone, testosterone, testosterone cypionate, testosterone enanthate or testosterone propionate.

13. A composition according to claim 10 wherein the estrogen is selected from the group consisting of chlorotrianisene, diethylstilbestrol, estradiol, estradiol cypionate, estradiol valerate, estrone, estrone sodium sulfate, estropipate, ethinyl estradiol, mestranol, quinestrol or sodium equilin sulfate.

14. A composition according to claim 10 wherein the progestin is selected from the group consisting of ethynodiol diacetate, gestodene, hydroxyprogesterone caproate, levonorgestrel, medroxyprogesterone acetate, megestrol acetate, norethindrone, norethindrone acetate, norethynodrel, norgestrel or progesterone.

15. A composition according to claim 10 wherein the antimuscarinic agent is selected from the group consisting of anisotropine, atropine, clidinium, cyclopentolate, dicyclomine, flavoxate, glycopyrrolate, hexocyclium, homatropine, ipratropium, isopropamide, mepenzolate, methantheline, oxyphencyclimine, pirenzepine, propantheline, scopolamine, telenzepine, tridihexethyl or tropicamide.

16. A device for the transdermal administration, at a therapeutically effective rate, of a drug, which device comprises:

- (a) a reservoir comprising a therapeutically effective amount of a drug and a skin permeation-enhancing amount of a permeation mixture comprising:
  - (i) 15 to 25% by weight of a monoglyceride or a mixture of monoglycerides, and
  - (ii) 8 to 25% by weight of a lactate ester or a mixture of lactate esters;
- (b) a backing on the skin-distal surface of the reservoir; and
- (c) means for maintaining the reservoir in drug- and permeation enhancing mixture-transmitting relation with the skin.

17. A device for the transdermal administration, at a therapeutically effective rate, of a drug, which device comprises:

- (a) a first reservoir comprising a therapeutically effective amount of drug and a skin permeation-enhancing amount of a permeation mixture comprising:
  - (i) 15 to 25% by weight of a monoglyceride or a mixture of monoglycerides, and
  - (ii) 8 to 25% by weight of a lactate ester or a mixture of lactate esters;
- (b) a second reservoir comprising an excess of the permeation enhancing mixture and drug at or below saturation;
- (c) a rate-controlling membrane between the first reservoir and the second reservoir;
- (d) a backing on the skin-distal surface of the second reservoir; and
- (e) means for maintaining the first and second reservoirs in drug- and permeation enhancing mixture-transmitting relation with the skin.

18. A device according to claim 16 or 17 wherein the monoglyceride is glycerol monolaurate.

19. A device according to claim 16 or 17 wherein the lactate ester is lauryl lactate.

20. A device according to claim 16 or 17 wherein the lactate ester is ethyl lactate.

21. A device according to claim 16 or 17 wherein the lactate ester is cetyl or myristyl lactate.

22. A device according to claim 16 or 17 wherein the mixture of lactate esters is ethyl and lauryl lactate.

23. A device according to claim 16 or 17 wherein the monoglyceride is glycerol monolaurate and the lactate ester is ethyl lactate or lauryl lactate or a mixture thereof.

24. A device according to claim 16 or 17 wherein the drug is selected from the group consisting of a benzodiazepine, an antimuscarinic agent, an estrogen, an androgen, or a progestin.

25. A device according to claim 16 or 17 wherein the drug is selected from the group consisting of alclometasone, aldosterone, amcinonide, beclomethasone dipropionate, betamethasone, clobetasol, clocortolone, cortisol, cortisone, corticosterone, desonide, desoximetasone, 11-desoxycorticosterone, 11-desoxycortisol, dexamethasone, diflorasone, fludrocortisone, flunisolide, fluocinolone, fluocinonide, fluorometholone, flurandrenolide, halcinonide, hydrocortisone, medrysone, 6 $\alpha$ -methylprednisolone, mometasone, paramethasone, prednisolone, prednisone, tetrahydrocortisol or triamcinolone.

26. A device according to claim 16 or 17 wherein the drug is selected from the group consisting of danazol, fluoxymesterone, methandrostenolone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol, testolactone, testosterone, testosterone cypionate, testosterone enanthate or testosterone propionate.

27. A device according to claim 16 or 17 wherein the drug is selected from the group consisting of chlorotrianisene, diethylstilbestrol, estradiol, estradiol cypionate, estradiol valerate, estrone, estrone sodium

sulfate, estropipate, ethinyl estradiol, mestranol, quinestrol or sodium equilin sulfate.

28. A device according to claim 16 or 17 wherein the drug is selected from the group consisting of ethynodiol diacetate, gestodene, hydroxyprogesterone caproate, levonorgestrel, medroxyprogesterone acetate, megestrol acetate, norethindrone, norethindrone acetate, norethynodrel, norgestrel or progesterone.

29. A device according to claim 16 or 17 wherein the drug is selected from the group consisting of anisotropine, atropine, clidinium, cyclopentolate, dicyclomine, flavoxate, glycopyrrolate, hexocyclium, homatropine, ipratropium, isopropamide, mepenzolate, methantheline, oxyphenacyclimine, pirenzepine, propantheline, scopolamine, telenzepine, tridihexethyl or tropicamide.

30. A device according to claim 16 wherein the means for maintaining the reservoir in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the reservoir.

31. A device according to claim 17 wherein the means for maintaining the reservoirs in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the first reservoir.

32. A device according to claim 17 wherein the first reservoir also is an adhesive layer which functions as the means for maintaining the reservoirs in relation with the skin.

33. A device according to claim 19, 20, 21 or 22 wherein the monoglyceride is glycerol monolaurate.

34. A device according to claim 33 wherein the glycerol monolaurate and lactate esters comprise 20 wt % and 12 wt % of the drug containing reservoir, respectively.

35. A method for the transdermal administration of a drug, which method comprises:

- (a) administering the drug at a therapeutically effective rate to an area of skin; and
- (b) simultaneously administering a permeation enhancing mixture comprising:
  - (i) 15 to 25% by weight based on the drug and permeation enhancer mixture of a monoglyceride or a mixture of monoglycerides, and
  - (ii) 8 to 25% by weight based on the drug and permeation enhancer mixture of a lactate ester or a mixture of lactate esters;

to the area of skin at a rate which is sufficient to substantially increase the permeability of the area to the drug.

36. A method for the transdermal administration of a drug, the method comprising the step of placing a transdermal drug delivery device onto the skin of a person, the transdermal delivery device comprising:

- (a) a reservoir comprising drug in an amount sufficient to provide a therapeutic effect for an extended period of time and a permeation enhancing mixture comprising:
  - (i) 15 to 25% by weight of a monoglyceride or a mixture of monoglycerides, and
  - (ii) 8 to 25% by weight of a lactate ester or a mixture of lactate esters,in a skin permeation-enhancing amount;
- (b) a backing on the skin-distal surface of the reservoir; and



- (c) means for maintaining the reservoir in drug- and permeation enhancing mixture-transmitting relation with the skin.

37. A method for the transdermal administration of a drug, the method comprising the step of placing a transdermal drug delivery device onto the skin of a person, the transdermal delivery device comprising:

- (a) a first reservoir comprising a therapeutically effective amount of drug and a skin permeation-enhancing amount of a permeation mixture comprising:
  - (i) 15 to 25% by weight of a monoglyceride or a mixture of monoglycerides, and
  - (ii) 8 to 25% by weight of a lactate ester or a mixture of lactate esters;
- (b) a second reservoir comprising an excess of the permeation enhancing mixture and drug at or below saturation;
- (c) a rate-controlling membrane between the first reservoir and the second reservoir;
- (d) a backing on the skin-distal surface of the second reservoir; and
- (e) means for maintaining the first and second reservoirs in drug- and permeation enhancing mixture-transmitting relation with the skin.

38. A method according to claim 35, 36 or 37 wherein the monoglyceride is glycerol monolaurate.

39. A method according to claim 35, 36 or 37 wherein the lactate ester is lauryl lactate.

40. A method according to claim 35, 36 or 37 wherein the lactate ester is ethyl lactate.

41. A method according to claim 35, 36 or 37 wherein the lactate ester is cetyl or myristyl lactate.

42. A method according to claim 35, 36, or 37 wherein the mixture of lactate esters is ethyl and lauryl lactate.

43. A method according to claim 35, 36 or 37 wherein the monoglyceride is glycerol monolaurate and the lactate ester is ethyl lactate or lauryl lactate or a mixture thereof.

44. A method according to claim 35, 36 or 37 wherein the drug is selected from the group consisting of a benzodiazepine, an antimuscarinic agent, an estrogen, an androgen, or a progestin.

45. A method according to claim 36 or 37 wherein the monoglyceride is glycerol monolaurate and the glycerol monolaurate and lactate esters comprise 20 wt % and 12 wt% of the drug containing reservoir, respectively.

46. A method according to claim 35 wherein the monoglyceride is glycerol monolaurate and the glycerol monolaurate and lactate esters comprise 20 wt% and 12 wt%, respectively or the drug and permeation enhancer mixture.

1/8

FIG. 1

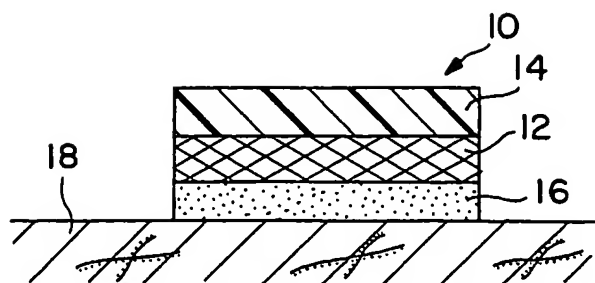


FIG. 2

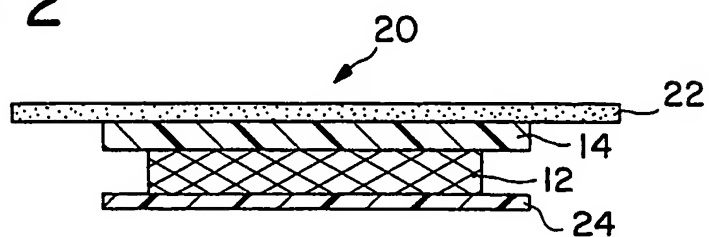


FIG. 3

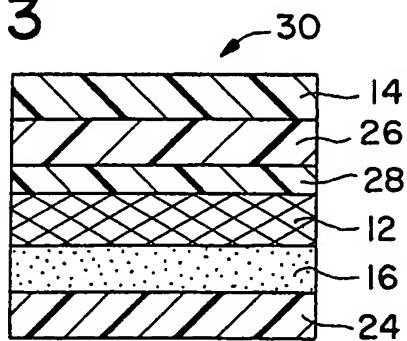
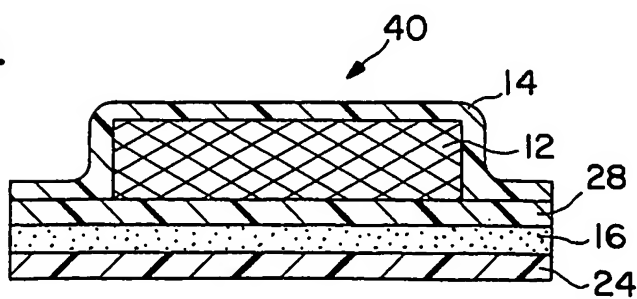


FIG. 4



2/8

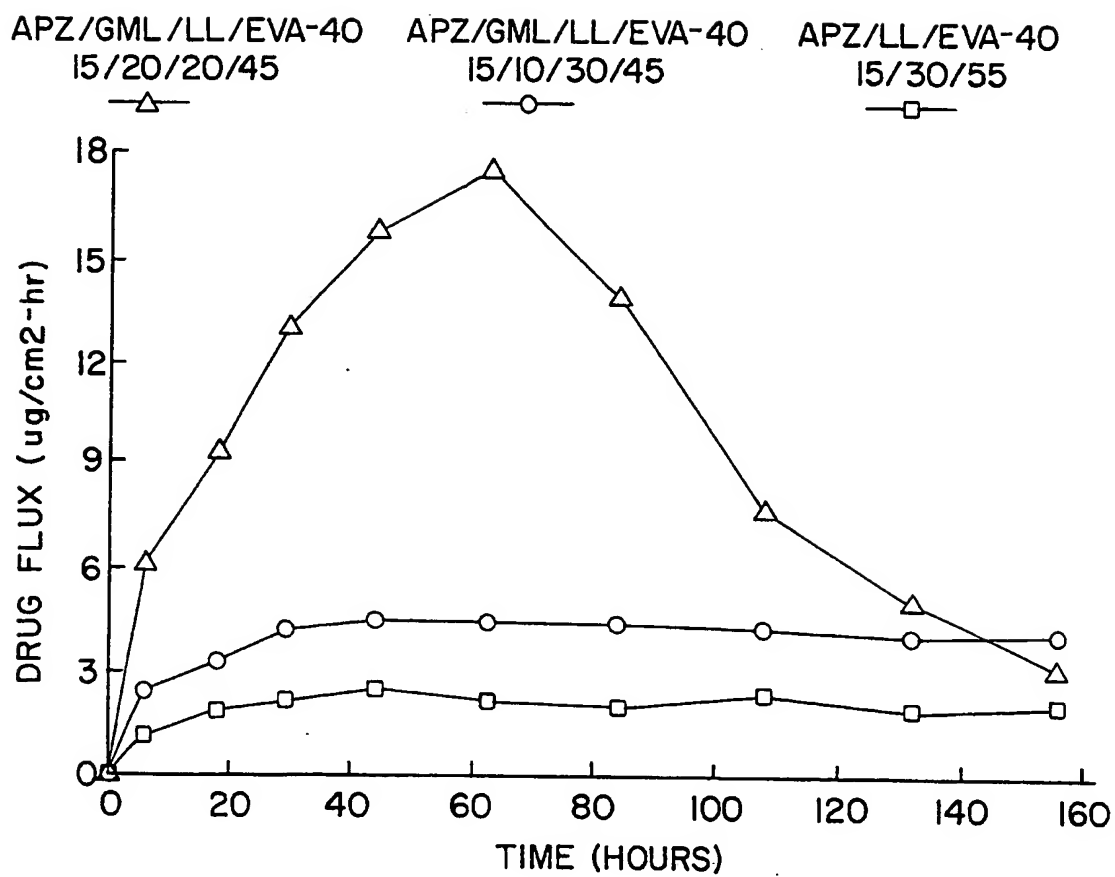
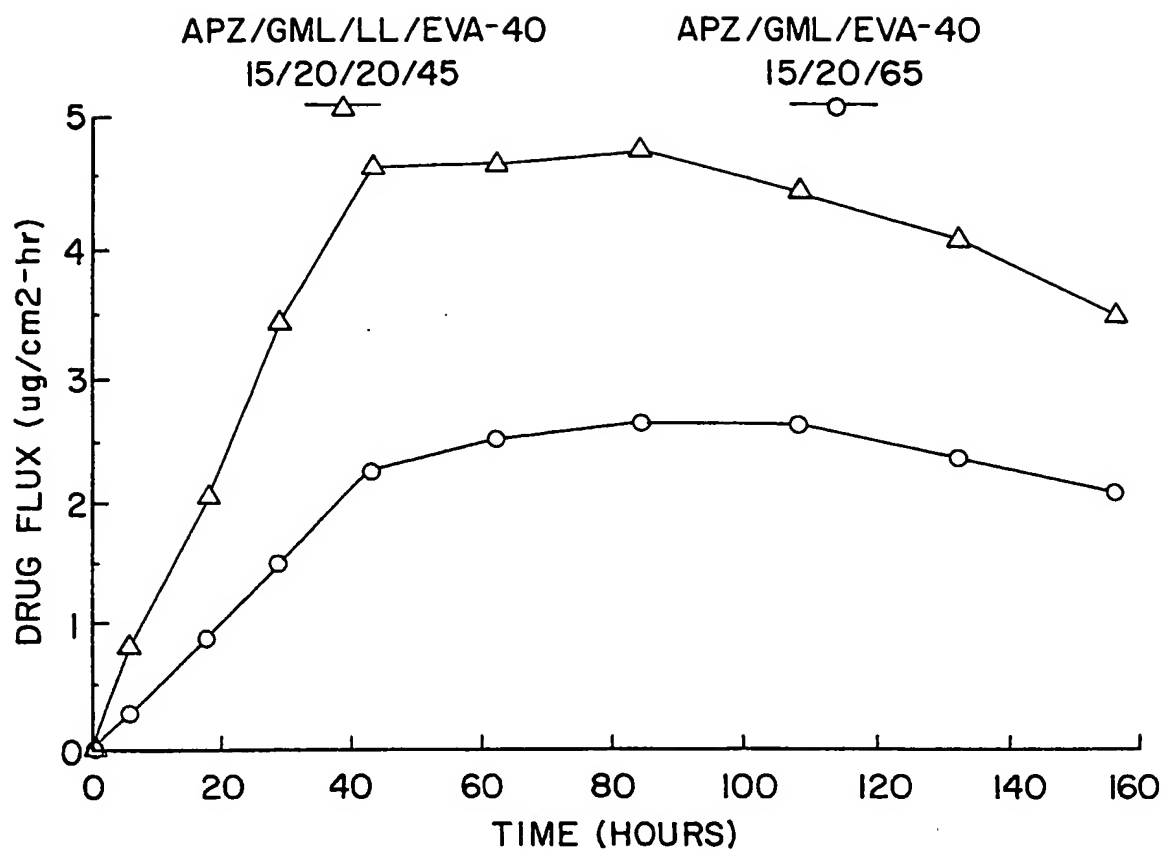


FIG. 5

3/8

**FIG. 6**

4/8

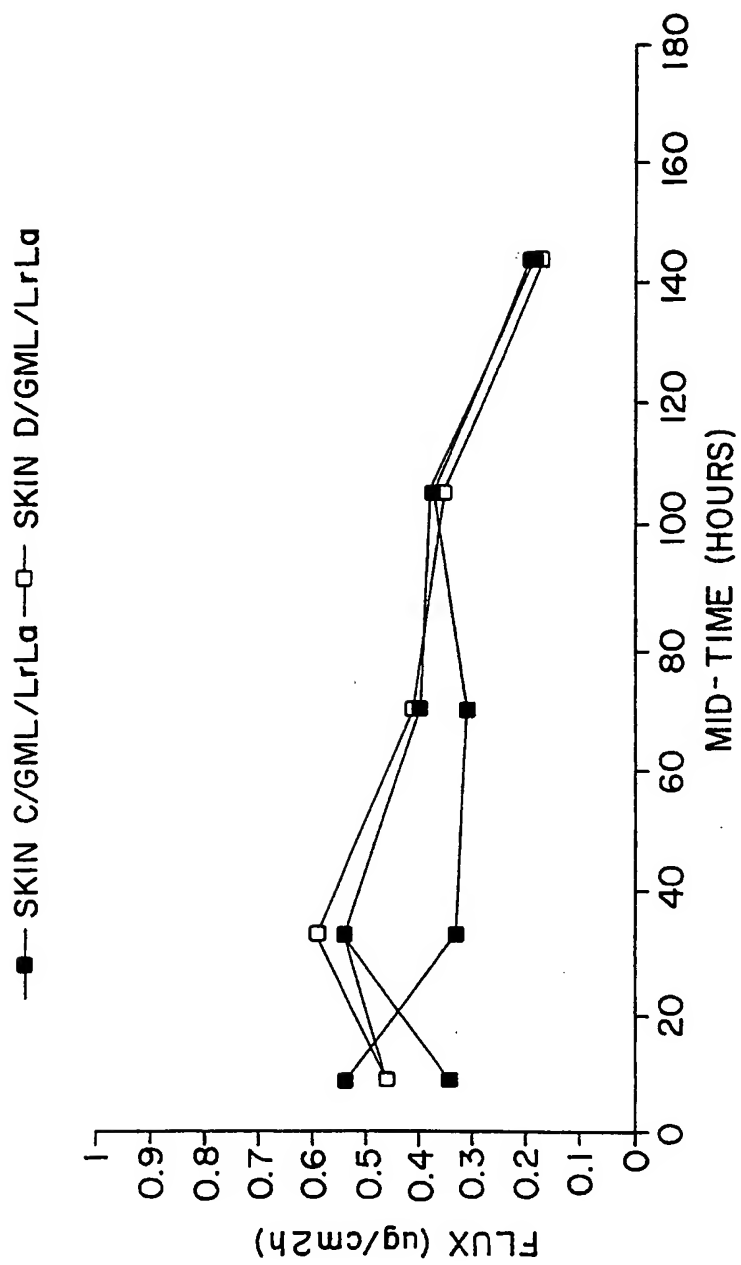


FIG. 7

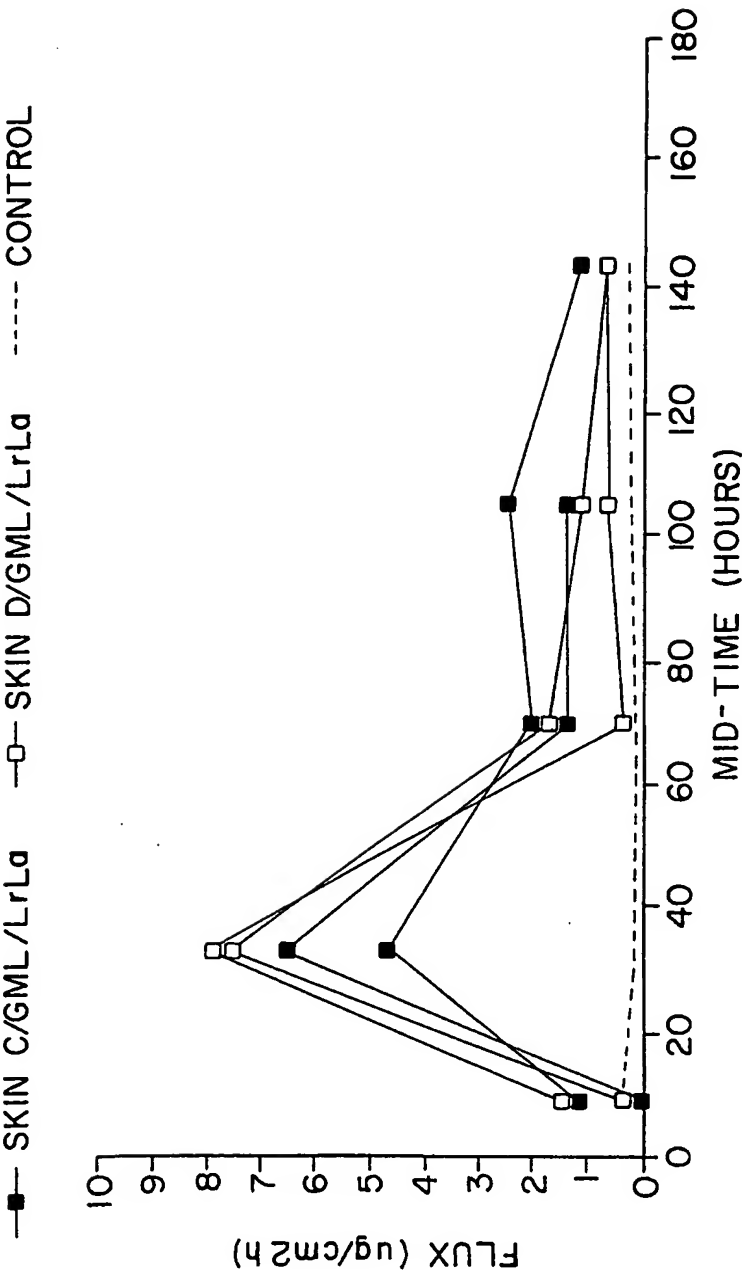


FIG. 8

6/8

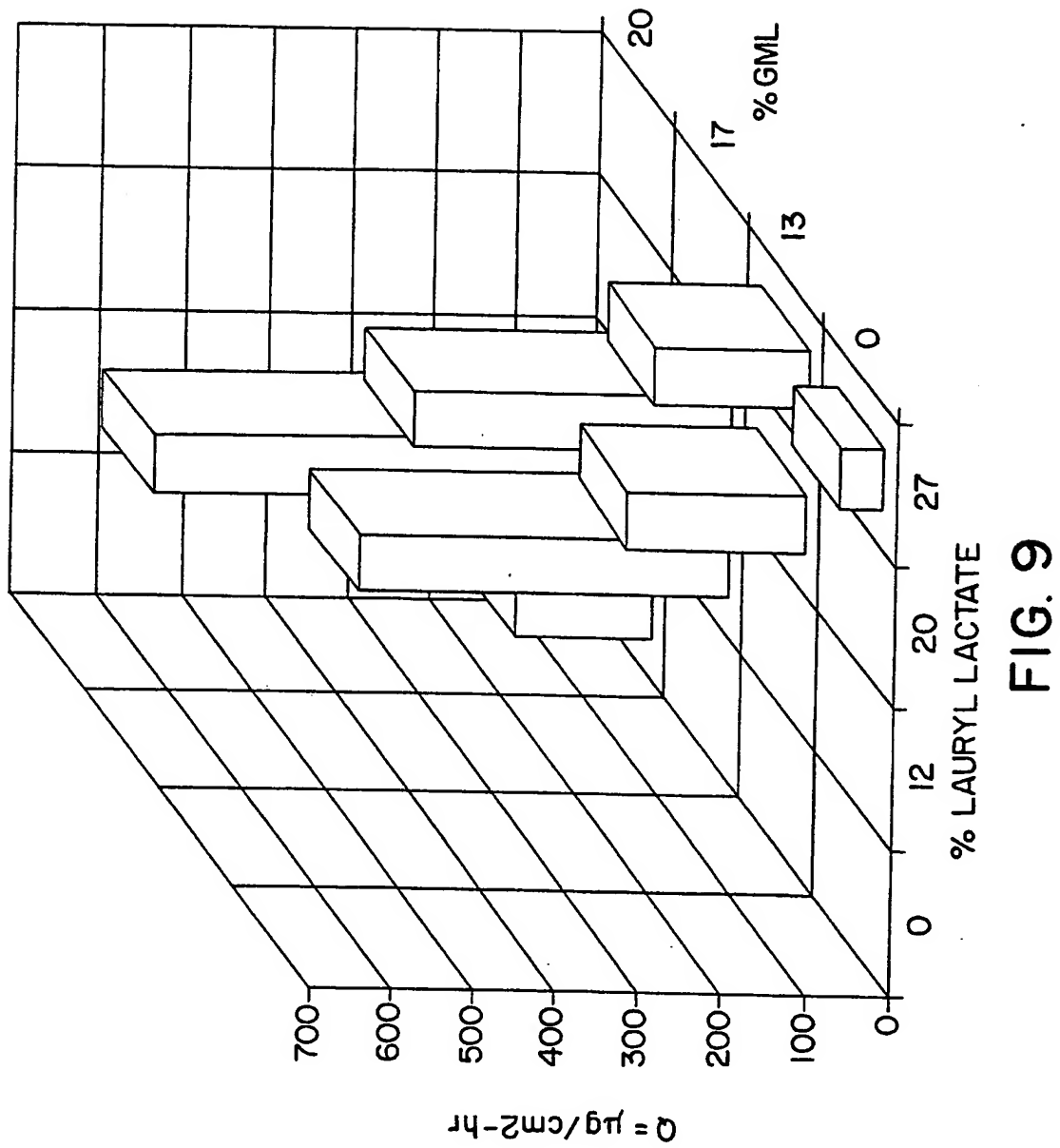


FIG. 9



7/8

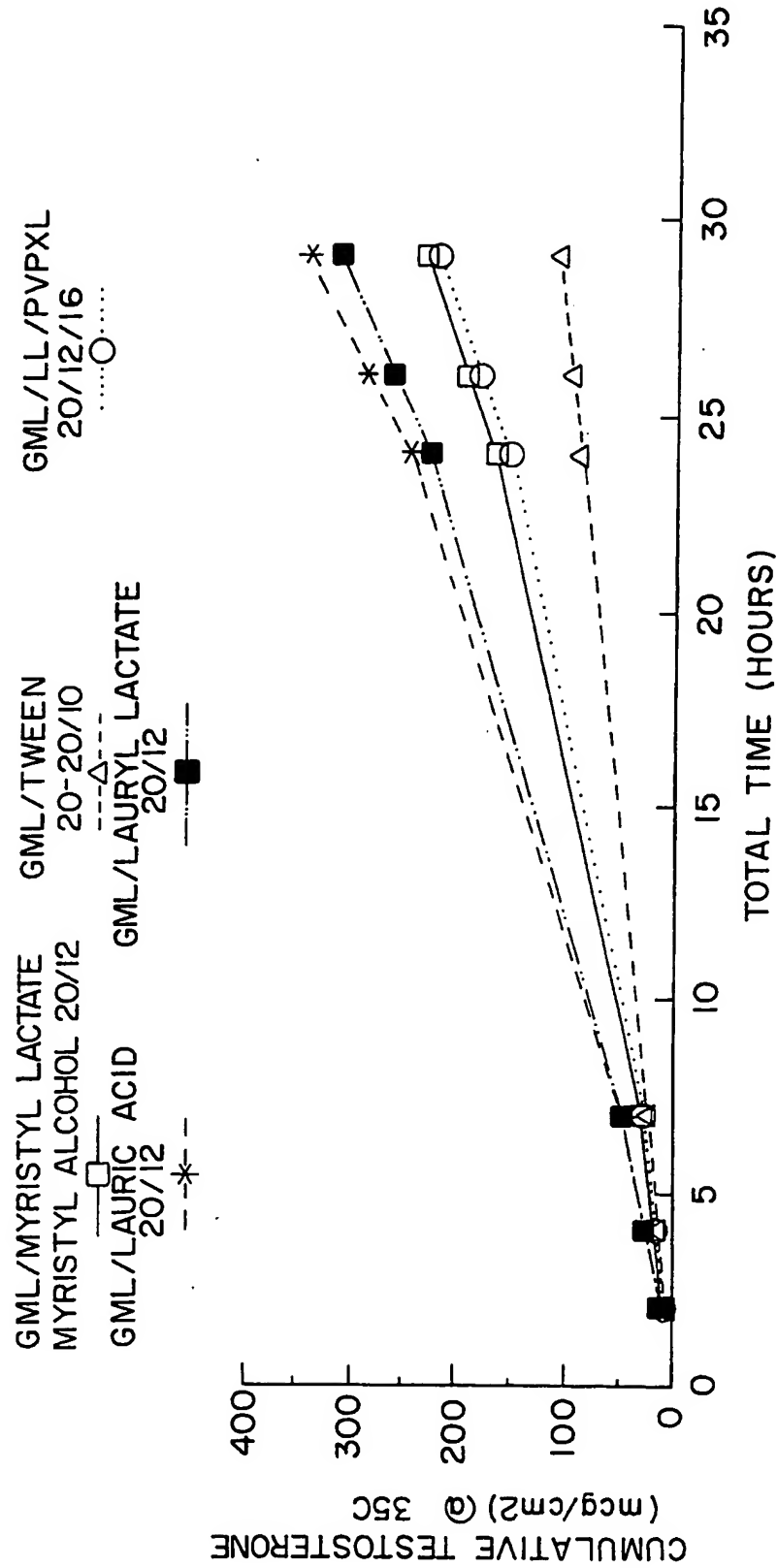


FIG. 10

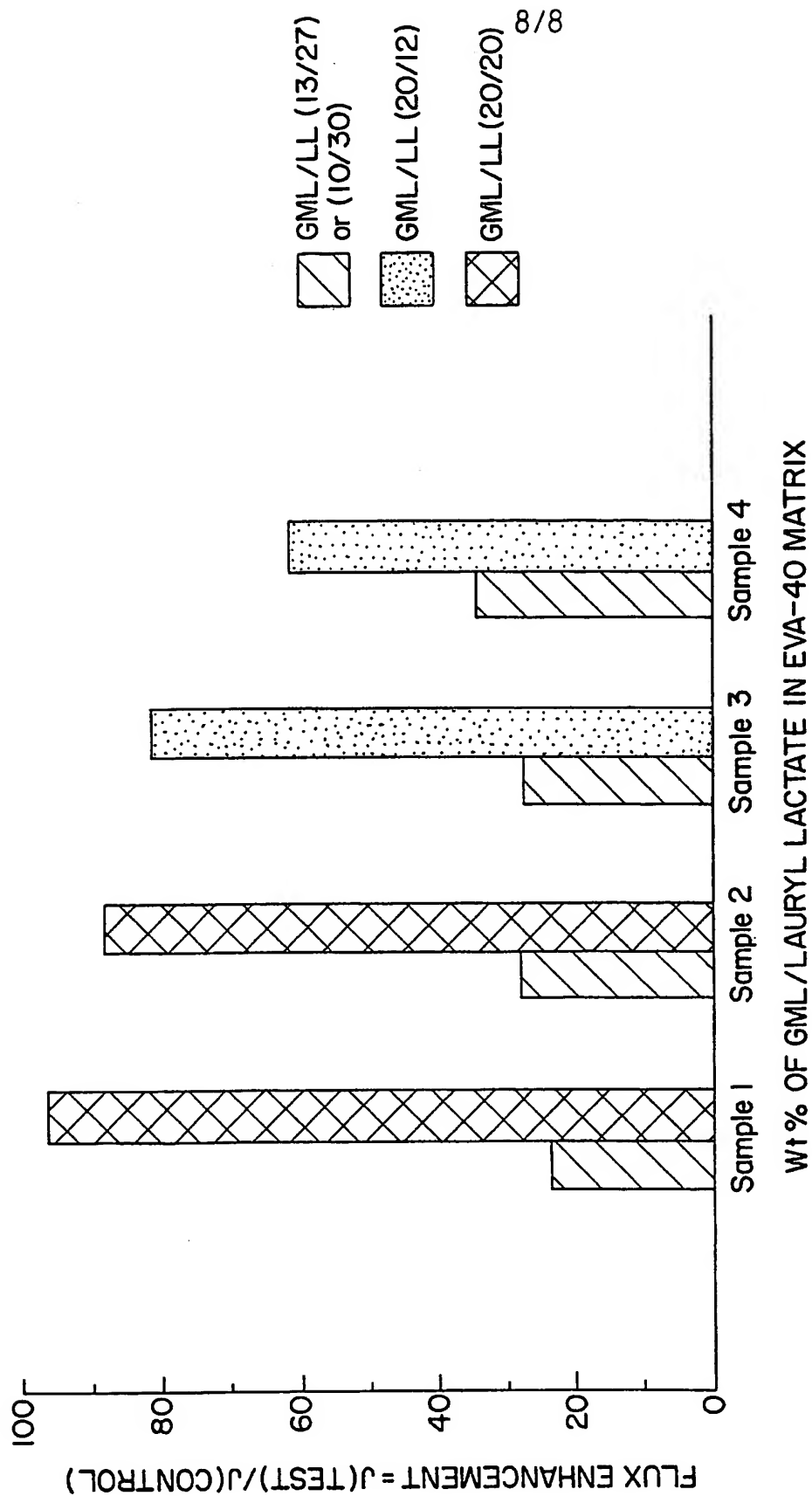


FIG. 11

## INTERNATIONAL SEARCH REPORT

 Internat Application No  
 PCT/US 94/11120

 A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K47/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 431 942 (SANSHO CO. LTD.) 12 June 1991  see claims 1,4,5 see page 6, line 17 - line 27 ---	1-3,5,6, 8,9, 16-19, 21,23, 30-39, 41-46
A	EP,A,0 368 339 (EISAI CO. LTD.) 16 May 1990 cited in the application  see claims 1,5,8 see page 3, line 11 - line 12 --- -/--	1-3,5,6, 8,9, 16-19, 21,23, 30-39, 41-46

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \* "A" document defining the general state of the art which is not considered to be of particular relevance
- \* "E" earlier document but published on or after the international filing date
- \* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \* "O" document referring to an oral disclosure, use, exhibition or other means
- \* "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

8 February 1995

Date of mailing of the international search report

22.02.95

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+31-70) 340-3016

Authorized officer

VENTURA AMAT, A

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/11120

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP,A,0 295 411 (SANSHO CO. LTD.) 21 December 1988 cited in the application</p> <p>see claims 1,6 see page 3, line 9 - line 11 -----</p>	<p>1-3,5,6, 8,9, 16-19, 21,23, 30-39, 41-46</p>

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/11120

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0431942	12-06-91	JP-A-	3236317	22-10-91
		CA-A-	2031243	07-06-91
		DE-D-	69007592	28-04-94
		DE-T-	69007592	13-10-94
		US-A-	5246949	21-09-93
-----				
EP-A-0368339	16-05-90	JP-A-	2131426	21-05-90
		AU-B-	615115	19-09-91
		AU-A-	4384589	17-05-90
		CA-A-	2001574	11-05-90
		DE-T-	68907312	25-11-93
		ES-T-	2057064	16-10-94
		FI-B-	92149	30-06-94
		NO-B-	176082	24-10-94
		US-A-	5041437	20-08-91
-----				
EP-A-0295411	21-12-88	JP-A-	1052716	28-02-89
		DK-B-	169016	01-08-94
		FI-B-	91361	15-03-94
		NO-B-	175515	18-07-94
		US-A-	5059427	22-10-91
		US-A-	5073375	17-12-91
-----				

**THIS PAGE BLANK (USPTO)**